TITLE: A low glycemic index meal and bedtime snack prevents post-prandial hyperglycemia and associated rises in inflammatory markers, providing protection from early but not late nocturnal hypoglycemia following evening exercise in type 1 diabetes

Author

Matthew D Campbell[1] BSc, Mark Walker[2] MD, Michael I Trenell[2] PhD, Emma J Stevenson[1] PhD, Daniel Turner[3] BSc, Richard M Bracken[3] PhD, James A Shaw[2] FRCP, Daniel J West[1] PhD.

Affiliation

[1]Faculty of Health and Life Sciences, Northumbria University, Newcastle-upon-Tyne, UK; [2]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, UK; [3]Applied Sports, Technology, Exercise and Medicine Research Centre, College of Engineering, Swansea University, Swansea, UK

Corresponding author

Daniel J West

Faculty of Health and Life Sciences, Northumberland Building, Northumbria University, Northumberland Road, Newcastle-upon-Tyne, NE1 8ST, UK.

Tel: 0044+ (0)191 243 7086

Email: d.j.west@northumbria.ac.uk

Running title: Glycaemic index of post-exercise foodstuffs

Clinical trials number: NCT01794650, ClinicalTrials.gov

Word count: abstract 249, manuscript 3798

No. of tables/figures: 3 Figures, 1 Table

ABSTRACT

OBJECTIVE: To examine the influence of the glycemic index (GI) of foods consumed after evening-exercise on post-prandial glycemia, metabolic and inflammatory markers, and nocturnal glycemic control in type 1 diabetes. **RESEARCH DESIGN AND METHODS**: On two evenings (~17:00 P.M.) ten male patients (27±1 years, HbA_{1c} 6.7±0.2% / 49.9±2.4mmol/mol) administered a 25% rapid-acting insulin dose with a carbohydrate bolus 60 minutes prior to 45 minutes of treadmill running. At 60 minutes post-exercise, patients administered a 50% rapid-acting insulin dose with one of two isoenergetic meals (1.0g.carbohdyrate.kg^{-1}BM) matched for macronutrient content but of either low (**LGI**) or high (**HGI**) GI. At 180 minutes post-meal, **LGI** ingested a low GI snack, and **HGI** a high GI snack (0.4g.carbohdyrate.kg^{-1}BM), before returning home (~23:00 P.M.). Interval samples for blood glucose and lactate; plasma glucagon, epinephrine, IL-6 and TNF-α; and serum insulin, cortisol, NEFA, and β-hydroxybutyrate assay were obtained. Interstitial glucose was recorded for 20 hours post-laboratory attendance using continuous-glucose monitoring. **RESULTS**: Following the post-exercise meal, **HGI** induced hyperglycemia in all patients (mean glucose [mean±SEM]: **HGI** 13.5±1.2 mmol.L^{-1}) and marked increases in TNF-α and IL-6; whereas relative euglycemia was maintained with **LGI** (7.7±0.8 mmol.L^{-1}; p<0.001) without inflammatory cytokine elevation. Both meal types protected all patients from early hypoglycemia. Over-night glycemia was comparable with similar incidence of nocturnal hypoglycemia (**HGI**=4; **LGI**=4 patients). **CONCLUSIONS**: Consuming low GI foods with a reduced rapid-acting insulin dose following evening exercise prevents post-prandial hyperglycemia and inflammation, and provides hypoglycemia protection for ~8 hours post-exercise; however, risk of late nocturnal hypoglycemia remains.

There is a growing evidence base surrounding the wide range of health benefits from regular exercise, for type 1 diabetes patients (1). However, exercise remains the most frequently identified specific cause of severe hypoglycemia (2), the fear of which, remains the primary obstacle to patients wishing to engage in regular exercise (3).

Strategies to combat exercise-induced hypoglycemia, such as manipulating exercise intensity (4), insulin dose and diet (5-7), or order in which different exercise types are undertaken (8), have predominantly been trialled for morning-time exercise (5-7). However, many individuals prefer to exercise in the evening due to study / work commitments or for social reasons. Unfortunately, exercise in the evening is associated with a greater risk of post-exercise hypoglycemia (4; 9), with low blood glucose levels likely to occur particularly nocturnally (2). Incorporation of evening exercise safely into the lives of people with type 1 diabetes is thus significantly hampered by the lack of appropriate evidence necessary for informed self-management strategies.

We recently demonstrated that meal time insulin adjustment, specifically reducing the dose of rapid-acting insulin before and after exercise, is vital to minimise risk of post-exercise hypoglycemia (5). However, there is currently little advice on optimal carbohydrate type for exercising patients with type 1 diabetes (1). American Diabetes Association guidance focuses on the *quantity* rather than the *composition* of the carbohydrate to be consumed following exercise (10). Consumption of ~5 grams carbohydrate per kg body mass (BM) is typically recommended for moderate intensity exercise (11; 12), however, the food composition is also an important consideration, as the type of carbohydrate can exert a major influence on post-prandial glycemia in diabetes patients (13). Meals containing identical macronutrient compositions are digested and absorbed at varying rates producing a range of glycemic responses (14), with carbohydrate foodstuffs with a low glycaemic index (GI) eliciting a more gradual rise and fall in blood glucose compared to their high GI equivalents. Resultantly, more favorable post-prandial glycemic profiles have been shown following ingestion of low GI foods in patients with type 1 diabetes (15; 16).

It may thus be possible to optimize post-exercise glycemia by manipulating the composition of foods consumed during this time. The protracted absorption rates of low GI foods may be beneficial for reducing post-prandial hyperglycemia. However, slower delivery of carbohydrate to post-exercise musculature, and potentially slower rates of muscle glycogen replenishment following exercise (17; 18), may increase the risk of post-exercise hypoglycemia (11; 19). Inversely, consuming high GI foods may promote accelerated muscle glycogen restoration (17; 18), reducing the incidence of post-exercise hypoglycemia (11; 19). However, the need to reduce insulin- to carbohydrate -ratio may be associated with post-prandial hyperglycemia following ingestion of high GI foodstuffs (15; 16), potentially leading to metabolic, hormonal, and inflammatory disturbances (20-22).

The aim of this study was to examine the influence of the glycemic index of the meal and subsequent bedtime snack consumed after evening-time exercise on post-prandial glycemia, metabolism and circulating inflammatory markers, in addition to nocturnal glycemic control in type 1 diabetes.

RESEARCH DESIGN AND METHODS

Patients

Eligibility criteria comprised of being aged between 18 and 35 years with a duration of diabetes >2 years upon enrollment, absence of diabetes-related complications including impaired awareness of hypoglycemia, and insulin therapy alone without any other medication. Ten males with type 1 diabetes were recruited ([mean±SEM] age 27±1 years, BMI 25.5±0.3, duration of diabetes 15±2 years, HbA_{1c} 6.7±0.2%, 49.9±2.4 mmol/mol, $\dot{V}O_{2peak}$ 52±1 ml.kg.min^{-1}). All patients had been treated on a stable basal-bolus regimen comprising of insulin aspart and once-daily insulin glargine for a minimum of 6 months. 50% of patients were injecting insulin glargine in the morning, and 50% in the late evening / before bed. All patients undertook regular and consistent exercise (participating in aerobic-based exercise for at least 30 minutes at a time, at least thrice weekly). All patients were familiar with carbohydrate counting, administering 1.0±0.1 units of insulin aspart per 10 g of carbohydrate.

Following approval from the local National Health Service Research Ethics Committee, fully informed written consent was gained from all patients. Firstly, patients attended the Newcastle NIHR Clinical Research Facility exercise laboratory for a preliminary screening visit, as described by Campbell et al. (2013), before returning on three further occasions. On visit 1, peak cardiorespiratory parameters were collected during the completion of an incremental-maximal treadmill run protocol, as previously described (5; 6). Computer randomization then determined the sequence of the two subsequent experimental visits.

Pre-laboratory phase

CGM

Patients were fitted with a continuous glucose monitor (CGM; Paradigm Veo, Medtronic diabetes, Northridge, CA, USA) using an Enlite sensor (Medtronic Minimed, Northridge, CA, USA), a minimum of 48 hours before attending the laboratory on each occasion. The Paradigm Veo (Medtronic Diabetes,

Northridge, CA, USA) provides real time glucose profiles as part of an insulin pump. Patients did not use the continuous subcutaneous insulin infusion facility however, continuing their usual basal-bolus regimen. Glucose alerts were set at $\leq$3.5 and $\geq$16 mmol.L^{-1} during the pre-trial period. The high glucose alert was discontinued once patients left the laboratory after experimental trials. Sensors were placed in the postero-lateral abdominal region to minimize the physiological time lag between blood and interstitial glucose (23). Insertion site was replicated across visits. During sensor wear, patients performed a minimum of 4 daily capillary blood glucose tests (GlucoMen LX; Menarini Diagnostics, Berkshire, UK), entering all values into the CGM device for calibration. Capillary glucose values and not CGM data were used to inform self-administered insulin aspart doses. Downloaded data were retrospectively processed and analyzed using CareLink Veo Professional software (Medtronic Diabetes, Northridge, CA, USA).

Diet and activity replication

Over the 24 hours preceding main trial visits, patients replicated their diet (assessed using weighed dietary recording sheets) and were instructed to maintain their normal insulin regimen, with basal dose standardized (dose, injection site, and time of injection) across trials. During this time, patients used a pedometer (Omron Healthcare Europe B.V., Hoofddrorp, Holland) to record total step count. Avoidance of strenuous exercise was required in the previous 48 hours, with maintenance of similar activity patterns between trials, which were separated by at least 7 days. On the day of the trial, patients were provided with two standardized meals, a cereal-based breakfast (frosted flakes, semi-skimmed milk, and peaches) equating to 1.3g.carbohdyrate.kg^{-1}BM (549±20 kcal) and a pasta-based lunch (pasta, tomato-based sauce, cheddar cheese, olive oil) equating to 1.3g.carbohdyrate.kg^{-1}BM (968±35 kcal). Meal compositions were based on the habitual dietary patterns of those with type 1 diabetes, and current recommendations for exercise in diabetes patients (11; 12). When combined with meals provided in the laboratory during experimental trials, total dietary intake across the day was calculated to constitute ~5.0g.carbohdyrate.kg^{-1} with a macronutrient content consisting of 77% carbohydrate, 12% fat and 11% protein (11; 12).

Testing procedure

Patients arrived at the laboratory in the late afternoon (~17:00 P.M.), replicating their start time across conditions. A 12-ml resting venous blood sample was taken of which 20µl was used for the immediate quantification of blood glucose and lactate (Biosen C-Line; EKF Diagnostic GmbH, London, UK) and 10 µl analyzed for hemoglobin and hematocrit (Hemo Control; EKF Diagnostic GmbH, UK) used to correct for changes in plasma volume (24). The remaining sample was aliquoted equally into Lithium-heparin (Vacuette, Greiner Bio-One GmBH, Austria) and serum separation tubes (Vacuette, Greiner Bio-One GmBH, Austria) that were centrifuged for 15 minutes at 3000 $rev.min^{-1}$ at 4˚C and stored at -80˚C for retrospective analysis of serum rapid-acting insulin analogue (Invitron Insulin Assay; Invitron, Monmouth, UK), cortisol (Parameter cortisol ELISA, R & D Systems, Roche Diagnostics, UK), non-esterified fatty acids (NEFA; Non-esterified fatty acids colorimetric assay, Ranbut; Randox Laboratories, London, UK), and β-hydroxybutyrate (D-3-hydroxybutyrate kinetic enzymatic assay, Ranbut; Randox Laboratories, London, UK), and plasma glucagon (Glucagon EIA, Sigma-Aldrich, USA), adrenaline (CAT ELISA, Eagle Biosciences, UK), interleukin-6 (IL-6; Human IL-6 Quantikine ELISA, R & D Systems, Roche Diagnostics, UK) and tumour necrosis factor alpha (TNF-α; Human TNF-alpha Quantikine ELISA, R & D Systems, Roche Diagnostics, UK). The coefficient of variation was <10% for all biochemical analysis.

Immediately after the resting sample, patients administered a 25% (2.0±0.1 units) dose (i.e., a 75% reduction) of insulin aspart into the abdomen with injection site standardized across trials, as equidistant between the iliac crest and naval, as currently recommended (5; 6; 25). Patients then consumed a pre-exercise carbohydrate bolus (frosted flakes, semi-skimmed milk, and peaches) equating to $1.0g.carbohdyrate.kg^{-1}BM$ (423±15 kcal), within a five-minute period (5).

Patients remained at rest for 60 minutes following consumption of the pre-exercise carbohydrate bolus. On 60 minutes, a blood sample was drawn immediately before commencing 45 minutes of treadmill

(Woodway, Weil am Rhein, Germany) running at a speed calculated to elicit 70% of their $\dot{V}O_{2peak}$, an intensity falling within recommendations of the American College of Sports Medicine (26) for exercising diabetes patients. Breath-by-breath respiratory parameters (MetaLyzer 3B; Cortex, Leipzig, Germany) and heart rate (S810; Polar, Kempele, Finland) were continuously recorded throughout exercise. Immediately following cessation of exercise, a blood sample was taken, with subsequent samples at 15, 30 and 60 minutes post-exercise. At 60 minutes post-exercise patients administered a 50% (4.0±0.2 units) dose of insulin aspart into the contralateral abdominal site to the pre-exercise insulin aspart injection (5). With this, in a random and counter-balanced fashion, patients consumed one of two evening meals calculated to be of either low or high GI. Following this meal, patients remained rested with further periodic blood samples every 30 minutes for 180 minutes. All patients then consumed a trial-specific bedtime snack of either low or high GI. Patients could drink water *ad libitum* throughout. All patients received transport home and were instructed to continue their usual basal insulin dose and replicate sleeping patterns as best possible across trials. Hypoglycemia was defined as a blood or interstitial glucose concentration of $\leq$3.9 mmol.L^{-1}, and hyperglycemia defined at glucose $\geq$8.0 mmol.L^{-1} (5).

Meal compositions and bedtime snack

All meals were pre-prepared by the research team and were composed of foodstuffs to elicit either a high or low GI response. We calculated the GI of each meal using methods described by Brouns et al (27) in 10 non-diabetes control participants. Patients consuming the low GI evening meal subsequently consumed the low GI bedtime snack, and those patients consuming the high GI evening meal consumed the high GI snack. Both evening meals and bedtime snacks were matched for macronutrient content, palatability, and had negligible fiber content (see supplemental table 1). Bedtime snacks equated to 0.4g.carbohdyrate.kg^{-1}BM (28).

Calculation of substrate oxidation

During exercise, at fifteen minutes before the post-exercise meal, and at 45, 105, and 165 minutes following the post-exercise meal, expired gases were analyzed (MetaLyzer 3B; Cortex, Leipzig, Germany). Substrate oxidation rates and energy expenditure were determined from oxygen consumption and carbon dioxide production values using stoichiometric equations (29).

Post-laboratory period

While wearing CGM, patients continued to self-record and replicate their diet throughout both trials using the weighed food diary. Patients were required to report additional carbohydrate ingestion and administration of corrective doses of insulin aspart. Patients were instructed to keep meal times, as well as insulin aspart and insulin and glargine doses consistent across trials.

Data analysis

Statistical analysis was performed using PASW *Statistics* software (IBM PASW version 18; IBM, Armonk, NY, USA). A repeated-measures ANOVA on two levels (condition and time) was conducted, with Bonferroni corrected pair-wise comparisons and paired samples *t*-test used to examine time and condition effects, respectively. Statistical significance was accepted at $p<0.05$. Area under the curve was calculated using the methods described by Wolever and Jenkins (30).

RESULTS

Pre-laboratory phase

Glycemic control was comparable over the 24 hours prior to patients' arrival at the laboratory for both experimental trials, (CGM mean glucose: **HGI** 7.9±0.7; **LGI** 7.9±0.7 mmol.L^{-1}, p=0.465; and total interstitial glucose area under the curve: **HGI** 11277±1069; **LGI** 10971±1126 mmol.L^{-1}.min^{-1}, p=0.215). Dietary intake was also similar during the 24 hours before both trials. There were no differences in total energy consumed (**HGI** 2143±673; **LGI** 2358±668 kcal, p=0.508), with similar contribution from carbohydrate (**HGI** 51±3; **LGI** 46±3 %, p=0.896), fat (**HGI** 30±3; **LGI** 32±4 %, p=0.301) and protein (**HGI** 20±2; **LGI** 22±3 %, p=0.556). The total amount of insulin administered (**HGI** 26±4; **LGI** 26±4 units, p=0.609) and levels of activity (**HGI** 6949±105; **LGI** 7041±118 steps, p=0.372) were comparable over the 24 hours before each trial.

Laboratory phase

There was a significant time effect (p<0.001), condition effect (p=0.05), and a significant condition*time interaction for absolute blood glucose concentrations (p<0.001; Figure 1). Blood glucose values were comparable before the standardized pre-exercise carbohydrate bolus / insulin injection and after the 1 hour pre-exercise rest period during both experimental trials (Figure 1). Serum insulin and all other hormones and metabolites were similar at rest and immediately before exercise (p>0.05; Figure 2A-B, Table 1).

Patients exercised at a similar intensity (%$\dot{V}O_{2peak}$: **HGI** 77±0.03; **LGI** 74±0.03, p=0.352; and HR_{peak}: **HGI** 80±2; **LGI** 79±3, p=0.631). Patients ran at a velocity of 10.1±0.3 km.hr^{-1}, completing 7.6±0.2 km and expending 718±48 kcal. Similar peak lactates were elicited immediately post-exercise (**HGI** 4.1±0.8; **LGI** 4.2±0.5 mmol.L^{-1}, p=0.137; Table 1). Exercise induced a similar decrease in blood glucose from pre-exercise concentrations (**HGI** -5.4±0.7; **LGI** -6.8±0.5 mmol.L^{-1}; p=0.733, Figure 1), such that

immediately following the cessation of exercise blood glucose were comparable to baseline under both conditions (p=0.304; Figure 1). There were no incidences of hypoglycemia during exercise, with all patients completing the exercise protocol on both occasions. Immediately before the post-exercise meal, serum insulin concentrations were similar to resting concentrations (p>0.05; Table 1), as were all other hormones, metabolites and cytokines (p>0.05; Figure 2A-C and Table 1).

Post-exercise intervention

Serum insulin peaked similarly at 60 minutes following the post-exercise meal, before declining under both conditions, with concentrations returning to resting values at 180 minutes (p>0.05; Table 1). Blood glucose levels increased over the 180 minutes after both post-exercise meals, but this was significantly attenuated under **LGI** in comparison to **HGI** (p<0.05; Figure 1). Over this time, all patients were protected from hypoglycemia under both conditions. However, all patients were exposed to hyperglycemia after the **HGI** meal, whereas this was limited to 4 patients after **LGI**. Moreover, hyperglycemia was less pronounced (mean peak blood glucose: **LGI** 8.8±1.0 vs. **HGI** 15.9±1.2 $mmol.L^{-1}$), and tended to be only transient (time spent hyperglycemic: **LGI** 81±26 vs. **HGI** 165±15 minutes) following the **LGI** meal. On leaving the laboratory, blood glucose remained significantly greater under after the **HGI** meal (**HGI** 12.7±1.5; **LGI** 7.5±2.6 $mmol.L^{-1}$, p=0.004; Figure 1), with more patients leaving the laboratory hyperglycemic (**HGI** n = 9, **LGI** n = 4).

Counter-regulatory hormonal and metabolic responses are presented in Table 1, with inflammatory cytokine and β-hydroxybutyrate responses in Figure 2A-C. There were no differences in serum β-hydroxybutyrate concentrations between the two experimental trials (p>0.05; Figure 2A). Following the post-exercise meal, IL-6 and TNF-α concentrations significantly increased from rest and pre-meal concentrations in the **HGI** trial, and were significantly greater than **LGI** during the post-prandial period (p<0.05; Figure 2B-C). During this period, concentrations in the **LGI** trial were significantly lower than baseline measures (p<0.05; Figure 2B-C).

There were no differences in substrate oxidation responses during the post-exercise meal period of both trials, with carbohydrate (**HGI** 14.5±2.6; **LGI** 14.7±2.7 g.carbohydrate.hr^{-1}, p=0.927) and lipid (**HGI** 3.0±0.9; **LGI** 3.1±0.9 g.lipid.hr^{-1}, p=0.809) oxidation rates similar.

Post-laboratory phase

Late Evening

After leaving the laboratory, interstitial glucose concentrations in the **HGI** trial were significantly greater than **LGI** in the time before sleep (Figure 3), with individualized mean peak interstitial glucose higher (**HGI** 18.3±1.1; **LGI** 13.9±0.8 mmol.L^{-1}, p=0.009).

Nocturnal glycemic control

During sleep, falling glucose levels were evident under both conditions such that concentrations became comparable 8 hours after exercise (p>0.05; Figure 3). Five patients during the **LGI** trial and 5 during the **HGI** trial were exposed to hypoglycemia, all of which occurred nocturnally. Some patients experienced multiple bouts of hypoglycemia, (**HGI** n = 10, **LGI** n = 8). Mean interstitial glucose nadir was similar between both conditions (**HGI** 3.6±0.4; **LGI** 3.4±0.3, p=0.650), as was time spent in hypoglycemic (p=0.569), euglycemic (p=0.705), and hyperglycemic (p=0.765) ranges (Figure 3).

Next day glycemic responses

On waking, interstitial glucose levels were comparable (**HGI** 8.5±0.9; **LGI** 8.3±0.9 mmol.L^{-1}, p=0.614; Figure 3), and glycemia remained similar between conditions for the remainder of the 24 hour post-exercise window (p>0.05).

During the post-laboratory period, total energy consumed (**HGI** 719±256, **LGI** 686±289 kcal, p=0.774), with contribution from carbohydrate (**HGI** 72±5; **LGI** 64±8 %, p=0.767), fat (**HGI** 20±5; **LGI** 22±7 %,

p=0.834), and protein (**HGI** 8±3; **LGI** 14±6 %, *p*=0.548) similar between conditions. Activity patterns for 24 hours after exercise were comparable (**HGI** 6086±94; **LGI** 6478±112 steps, *p*=0.369).

CONCLUSIONS

The aim of this study was to determine whether manipulating the glycemic index of foods consumed following evening-time exercise could modulate post-prandial glycemia and metabolism, to provide protection from post-exercise hyperglycemia and hypoglycemia in patients with type 1 diabetes. To our knowledge, this is the first study to show that consumption of low glycemic index foodstuffs, under conditions of reduced rapid-acting insulin dose following evening exercise, improves post-prandial glycemia, reducing hyperglycemia and concentrations of circulating inflammatory markers, in combination with protection from hypoglycemia for approximately 8 hours after exercise. However, beyond this time risk of late-onset nocturnal hypoglycemia persists regardless of the glycemic index of the post-exercise meal and bedtime snack.

We recently demonstrated the importance of reducing the rapid-acting insulin dose administered with the meal *after,* as well as before exercise to extend the period of protection from post-exercise hypoglycemia (5). Now we demonstrate that under these conditions, the composition of the post-exercise meal has an important role for modulating post-prandial glycemia. Blood glucose concentrations with the **HGI** post-exercise meal and snack were significantly greater than those with **LGI**, consequently exposing all patients in the former condition to hyperglycemia during the laboratory observation period. Conversely, the incidence of hyperglycemia was reduced by 60% after **LGI** (**LGI** = 40% vs. **HGI** = 100%). Indeed, in those patients affected, hyperglycemia was less pronounced and tended to be only transient and short lasting after **LGI** meals. Despite clear post-prandial differences in glycemia between the two conditions, all patients were still protected from hypoglycemia during their time in the laboratory. Presently, there are relatively few dietary guidelines to assist individuals with type 1 diabetes in managing post-exercise glycemia. However, we have shown that by consuming a low glycemic index post-exercise meal, post-prandial hyperglycemia can be reduced, without exposure to hypoglycemia. This is an important observation because the aim of diabetes management is to normalize blood glucose concentrations (31), especially when incorporating exercise into the lives of patients (1).

Given the potential for such large differences in post-prandial glycemia with this strategy, we examined this impact on metabolic, hormonal and inflammatory measures. This is important, as regular exposure to metabolic, hormonal or inflammatory disturbances could significantly influence long-term diabetes-related complications in regularly exercising patients (25). Here we show that meal GI has significant implications for post-prandial circulating inflammatory markers; specifically, we demonstrate for the first time, under non-clamp techniques and replicating free-living conditions, that the inflammatory cytokines TNF-α and IL-6 were dramatically increased following a high GI meal. An otherwise comparable low GI meal completely prevented rises in these inflammatory cytokines. The clinical relevance of these findings should not be underestimated, as offsetting hyperglycemia and inflammation is important for preventing early pathogenetic diabetes-related complications (22). Additionally, β-hydroxybutyrate concentrations did not significantly rise under either condition **(**Figure 2 A), remaining similar to pre-meal and resting concentrations. Basal insulin dose remained unchanged, and despite a reduction in rapid-acting insulin dose, circulating insulin concentrations remained sufficient for a suppression in β-hydroxybutyrate production (32) and to drive ketone body disposal (33). Concentrations during both trial conditions were well below those levels deemed clinically significant (>1.0 $mmol.L^{-1}$)(21).

When exercise is performed in the evening, consumption of a carbohydrate-based snack before bed is recommended (28). Blood glucose was typically within the euglycemic range prior to the consumption of the bedtime snack following **LGI**, but still hyperglycemic following **HGI** (**LGI** ~7.5 vs. **HGI** ~12.2 $mmol.L^{-1}$). Outside formal studies, patients within normal blood glucose ranges before bed often choose to raise blood glucose concentrations by consuming a carbohydrate-based snack (28) due to fear of nocturnal hypoglycemia (34). However, patients in the hyperglycemic range before bed may be tempted to administer corrective insulin units, which, in an exercise-induced insulin sensitized state (35; 36), is likely to cause a rapid fall in glucose during the night. Avoidance of the bedtime snack, and hence missing a valuable source of carbohydrate before sleep, is likely to exacerbate the risk of nocturnal hypoglycemia. Despite large differences in blood glucose concentrations before bed following **HGI** and

LGI in the current study, levels fell under both conditions becoming comparable 3 hours after consuming the bedtime snacks, with similar rates of nocturnal hypoglycemia thereafter. This indicates patients are at risk of late-onset nocturnal hypoglycemia despite the consumption of a bedtime snack, with predicted nadir more than 8 hours post-exercise (5; 9), and regardless of the GI of the snack or blood glucose levels before bed.

So that we could investigate the impact of the GI of the evening foodstuffs, patients consumed enough carbohydrate (consuming 2.6 g.carbohdyrate.kg^{-1} during the evening) to cover the cost of the exercise bout, with patients utilizing ~1.7 g.carbohdyrate.kg^{-1} in total during exercise, and with total daily carbohydrate intake matching current recommendations (~5.0g.carbohdyrate.kg^{-1}; (11; 12), thus establishing a positive carbohydrate balance. Despite consuming sufficient carbohydrate for the recovery of muscle glycogen post-exercise, and perhaps even consuming more carbohydrate than is typical, hypoglycemia was still encountered late after exercise in the early hours of the morning. These findings direct attention towards the role of basal insulin administration in avoiding nocturnal hypoglycemia after evening exercise. Considering once daily insulin glargine administration is associated with a glucose nadir 4-14 hours after administration (37; 38), not only basal insulin dose but also the timing of administration may be of particular importance.

This study shows for the first time that consuming low glycemic index foods, in tandem with reduced rapid-acting insulin dose, following evening exercise can play an important role in normalizing glycemia, preventing post-prandial hyperglycemia and inflammation, whilst protecting patients from post-exercise hypoglycemia for up to 8 hours. The clinical utility of these findings is clear, as foodstuffs which are part of a patients habitual diet can be easily exchanged with those that offer the same macronutrient content but are of a low GI (e.g. substituting particular types of breads, strains of rice, pastas and potatoes), facilitating more desirable post-prandial glycemic responses. However, it does not seem that carbohydrate type, nor total carbohydrate intake alone, are factors in the development of late-onset hypoglycemia, as

patients may still be exposed to nocturnal hypoglycemia following evening-time exercise. Future research is planned focusing on basal insulin adjustment to determine whether late-onset nocturnal hypoglycemia following evening-time exercise can be avoided, whilst harnessing the benefits of consuming low GI foodstuffs, with a reduced rapid-acting insulin dose, during the post-exercise period.

M.D.C. contributed to the conception and design of the study, researched data and wrote the manuscript. M.W. aided in participant recruitment and reviewed/edited the manuscript. M.I.T. aided in data collection and reviewed/edited the manuscript. E.J.S. aided in data collection and reviewed/edited the manuscript. D.T. contributed to the analysis of CGM data and reviewed/edited the manuscript. R.M.B. contributed to the analysis of CGM data and aided in preparation of the manuscript. J.A.S. aided in participant recruitment and reviewed/edited the manuscript. D.J.W. contributed to the conception and design of the study, aided researching data, and contributed to the writing of the manuscript. D.J.W. is the guarantor of this work and, as such, had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis.

ACKNOWLEDGEMENTS

This study was partially funded by Beneo. Continuous glucose monitoring equipment was provided by Medtronic Europe. Neither party had any role in the design of this study or the preparation of the manuscript. The authors thank the study participants for their time, effort and commitment, and the research team at the NIHR Clinical Research Facility, Newcastle University, for their assistance.

DUALITY OF INTEREST

There are no potential conflicts of interest to declare.

REFERENCES

1. Chu L, Hamilton J, Riddell MC: Clinical management of the physically active patient with type 1 diabetes. Phys Sports Med 2011;39:64-77

2. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R: Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. J Pediatr 2010;157:784-788

3. Brazeau AS, Rabasa-Lhoret R, Strychar I, Mircescu H: Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108-2109

4. Davey RJ, Bussau VA, Paramalingam N, Ferreira LD, Lim EM, Davis EA, Jones TW, Fournier PA: A 10-s Sprint Performed After Moderate-Intensity Exercise Neither Increases nor Decreases the Glucose Requirement to Prevent Late-Onset Hypoglycemia in Individuals With Type 1 Diabetes. Diabetes Care 2013:DC_122198

5. Campbell MD, Walker M, Trenell MI, Jakovljevic DG, Stevenson EJ, Bracken RM, Bain SC, West DJ: Large Pre-and Postexercise Rapid-Acting Insulin Reductions Preserves Glycemia and Prevents Early-but Not Late-Onset Hypoglycemia in Patients With Type 1 Diabetes. Diabetes Care 2013;36:2217-2224

6. West DJ, Morton RD, Bain SC, Stephens JW, Bracken RM: Blood glucose responses to reductions in pre-exercise rapid-acting insulin for 24 h after running in individuals with type 1 diabetes. J Sports Sci 2010;28:781-788

7. West DJ, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R, Bracken RM: A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. J Sports Sci 2011;29:279-289

8. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, Boulay P, Khandwala F, Sigal RJ: Resistance Versus Aerobic Exercise Acute effects on glycemia in type 1 diabetes. Diabetes Care 2013;36:537-542

9. McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, Fournier PA, Jones TW: Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. J Clin Endocrinol Metab 2007;92:963-968

10. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD: Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 2008;31:S61-S78

11. Riddell MC, Perkins BA: Type 1 diabetes and vigorous exercise: applications of exercise physiology to patient management. Can J Diabetes 2006;30:63-71

12. Perry E, Gallen I: Guidelines on the current best practice for the management of type 1 diabetes, sport and exercise. Practical Diabetes International 2009;26:116-123

13. Parillo M, Riccardi G: Dietary carbohydrates and glucose metabolism in diabetic patients. Diabetes Met 1995;21:391-401

14. Jenkins D, Wolever T, Taylor RH, Barker H, Fielden H, Baldwin JM, Bowling AC, Newman HC, Jenkins AL, Goff DV: Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362-366

15. Nansel TR, Gellar L, McGill A: Effect of varying glycemic index meals on blood glucose control assessed with continuous glucose monitoring in youth with type 1 diabetes on basal-bolus insulin regimens. Diabetes Care 2008;31:695-697

16. Parillo M, Annuzzi G, Rivellese A, Bozzetto L, Alessandrini R, Riccardi G, Capaldo B: Effects of meals with different glycaemic index on postprandial blood glucose response in patients with Type 1 diabetes treated with continuous subcutaneous insulin infusion. Diabetic Med 2011;28:227-229

17. Jensen TE, Richter EA: Regulation of glucose and glycogen metabolism during and after exercise. J Physiol 2012;590:1069-1076

18. Jentjens R, Jeukendrup AE: Determinants of post-exercise glycogen synthesis during short-term recovery. Sports Med 2003;33:117-144

19. MacDonald MJ: Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care 1987;10:584-588

20. Wallace T, Matthews D: Recent advances in the monitoring and management of diabetic ketoacidosis. QJM 2004;97:773-780

21. Laffel L: Ketone bodies: a review of physiology, pathophysiology and application of monitoring to diabetes. Diabetes Metab Rev 2000;15:412-426

22. Rosa JS, Oliver SR, Flores RL, Ngo J, Milne GL, Zaldivar FP, Galassetti PR: Altered inflammatory, oxidative, and metabolic responses to exercise in pediatric obesity and type 1 diabetes. Pediatric diabetes 2011;12:464-472

23. Keenan DB, Mastrototaro JJ, Zisser H, Cooper KA, Raghavendhar G, Lee SW, Yusi J, Bailey TS, Brazg RL, Shah RV: Accuracy of the Enlite 6-day glucose sensor with guardian and Veo calibration algorithms. Diabetes Technol Ther 2012;14:225-231

24. Dill D, Costill DL: Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. J App Physiol 1974;37:247-248

25. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson JL: Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care 2001;24:625-630

26. ACSM: Clinical Exercise Testing. In *ACSM's guidelines for exercise testing and prescription,* 8th ed. Walter R, Gordon NF, Pescatello LS, Eds. Baltimore, American College of Sports Medicine, 2010

27. Brouns F, Bjorck I, Frayn K, Gibbs A, Lang V, Slama G, Wolever T: Glycaemic index methodology. Nutr Res Rev 2005;18:145

28. Hernandez JM, Moccia T, Fluckey JD, Ulbrecht J, Farrell PA: Fluid snacks to help persons with type 1 diabetes avoid late onset postexercise hypoglycemia. Med Sci Sports Exerc 2000;32:904-910

29. Jeukendrup AE, Wallis GA: Measurement of substrate oxidation during exercise by means of gas exchange measurements. International Journal of Sports Medicine 2005;26 Suppl 1:S28-37

30. Wolever TM, Jenkins D: The use of the glycemic index in predicting the blood glucose response to mixed meals. Am J Clin Nutr 1986;43:167-172

31. Thomas D, Elliott EJ: Low glycaemic index, or low glycaemic load, diets for diabetes mellitus. Cochrane Database Syst Rev 2009;1

32. McGarry J: Ellenberg and Rifkin's Diabetes Mellitus. In *JAMA: J Am Med Assoc,* 5 ed. Porte D, R S, Eds. New York, McGraw-Hill, 1996, p. 19-28

33. Balasse EO, Féry F: Ketone body production and disposal: effects of fasting, diabetes, and exercise. Diabetes Metab Rev 1989;5:247-270

34. Cryer PE, Childs BP: Negotiating the barrier of hypoglycemia in diabetes. Diabetes Spectr 2002;15:20-27

35. Mikines KJ, Sonne B, Farrell P, Tronier B, Galbo H: Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol Endoc M 1988;254:E248-E259

36. Maarbjerg SJ, Sylow L, Richter E: Current understanding of increased insulin sensitivity after exercise - emerging candidates. Acta Physiologica Scand 2011;202:323-335

37. Ashwell S, Gebbie J, Home P: Optimal timing of injection of once-daily insulin glargine in people with Type 1 diabetes using insulin lispro at meal-times. Diabetic Med 2006;23:46-52

38. Thomas R, Aldibbiat A, Griffin W, Cox M, Leech N, Shaw J: A randomized pilot study in Type 1 diabetes complicated by severe hypoglycemia, comparing rigorous hypoglycemia avoidance with insulin analogue therapy, CSII or education alone. Diabetic medicine 2007;24:778-783

Table 1. Serum Insulin counter-regulatory hormonal and blood metabolite responses to post-exercise meals of differing glycemic index

															ANOVA *p*	
		Rest	**60**	**Exercise**	**0**	**15**	**30**	**Pre-Meal**	**30**	**60**	**90**	**120**	**150**	**180**	**T**	**T*C**
Serum Insulin ($pmol.L^{-1}$)	**HGI**	126±17	137±20		201±40†	138±22	128±21	105±15	179±34‡	180±32‡	143±21‡	127±22‡	95±17	94±18	<0.001	=0.992
	LGI	124±18	150±23		203±38†	137±23	125±20	102±15	172±35‡	174±34‡	144±20‡	126±16‡	105±17	98±17		
Plasma Glucagon ($pg.mL^{-1}$)	**HGI**	730±99	591±72†		682±68	760±83	768±94	833±117	953±155†	922±154†	872±145†	798±141	690±100‡	669±101‡	<0.001	=0.306
	LGI	733±130	611±75†		658±68	792±82	818±100	816±125	947±170†‡	937±159†‡	907±149†	862±141	806±120	840±139		
Plasma Adrenaline ($nmol.L^{-1}$)	**HGI**	0.09±0.01	0.15±0.03		0.55±0.10†	0.35±0.11†	0.15±0.03	0.15±0.04	0.17±0.02	0.16±0.03	0.11±0.04	0.09±0.02	0.11±0.03	0.08±0.02	=0.013	=0.497
	LGI	0.08±0.02	0.15±0.02		0.54±0.12†	0.28±0.10†	0.14±0.04	0.14±0.04	0.15±0.02	0.13±0.03	0.11±0.02	0.11±0.02	0.10±0.02	0.07±0.02		
Serum Cortisol ($nmol.L^{-1}$)	**HGI**	0.17±0.03	0.18±0.02		0.28±0.02†	0.33±0.04†	0.24±0.03†	0.19±0.02	0.14±0.02	0.14±0.02	0.13±0.02‡	0.11±0.01†‡	0.08±0.01†‡	0.08±0.01†‡	<0.001	=0.099
	LGI	0.17±0.03	0.15±0.02		0.24±0.03†	0.32±0.05†	0.23±0.04†	0.18±0.03	0.13±0.02‡	0.12±0.02‡	0.10±0.01†‡	0.10±0.01‡	0.10±0.01‡	0.09±0.01‡		
Serum NEFA ($mmol.L^{-1}$)	**HGI**	0.18±0.05	0.12±0.03		0.25±0.06	0.35±0.06†	0.43±0.11†	0.53±0.15†	0.37±0.07	0.24±0.06‡	0.24±0.07‡	0.27±0.11‡	0.27±0.09‡	0.35±0.13	=0.011	=0.514
	LGI	0.27±0.07	0.18±0.03		0.27±0.07	0.34±0.07†	0.33±0.07	0.39±0.10†	0.39±0.10†	0.27±0.07	0.24±0.05	0.24±0.05	0.27±0.05	0.30±0.05		
Blood Lactate ($mmol.L^{-1}$)	**HGI**	1.0±0.2	1.1±0.3		4.1±0.8†	2.1±0.5†	1.3±0.3	1.0±0.3	0.7±0.2	0.9±0.2	0.8±0.1	0.7±0.2	0.5±0.1	0.4±0.1†	=0.001	=0.129
	LGI	0.9±0.2	1.0±0.2		4.2±0.5†	1.7±0.3	1.2±0.3	1.±0.2	0.8±0.2†	1.0±0.2	1.1±0.2	1.2±0.2‡	0.6±0.2	0.5±0.2		

NOTE: Data presented as mean ± SEM. Test meal and insulin were administered immediately following rest and pre-meal sample points. * indicates significantly different between conditions ($p \leq 0.05$). † indicates significantly different from rest. ‡ indicates significantly different from pre-meal. Exercise commenced 60 minutes after rest. **T** = Time, **C** = Condition.

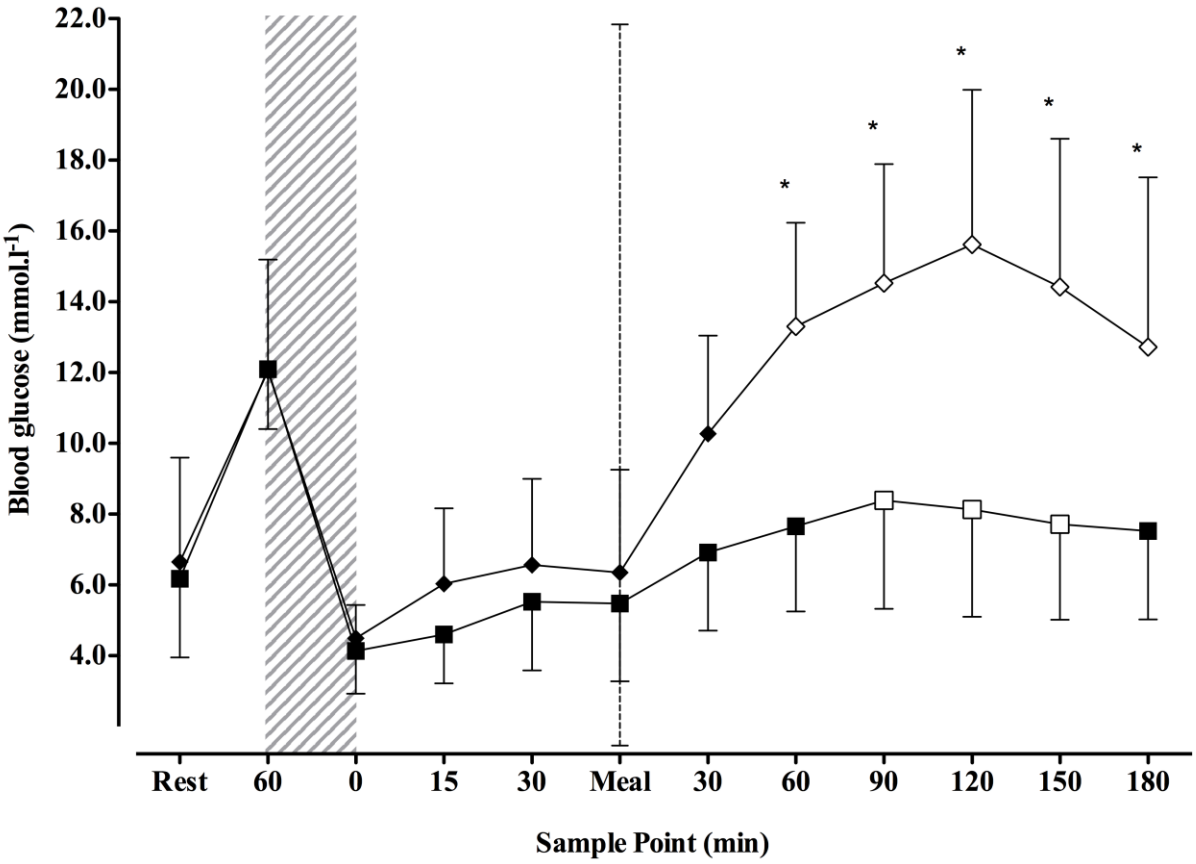

Figure 1. (**A**) Time-course changes in blood glucose from rest, during exercise and over the 3 hours post-exercise. Data are presented as mean ± SEM error bars. Squares = **LGI**, diamonds = **HGI**. Transparent markers indicate significant difference from pre-meal concentrations ($p \leq 0.05$). * indicates significant difference between conditions ($p \leq 0.05$). Thatched area indicates exercise; vertical dashed line indicates post-exercise meal intervention. NOTE: Test meal and insulin were administered immediately following rest and 60 minutes post-exercise sample points.

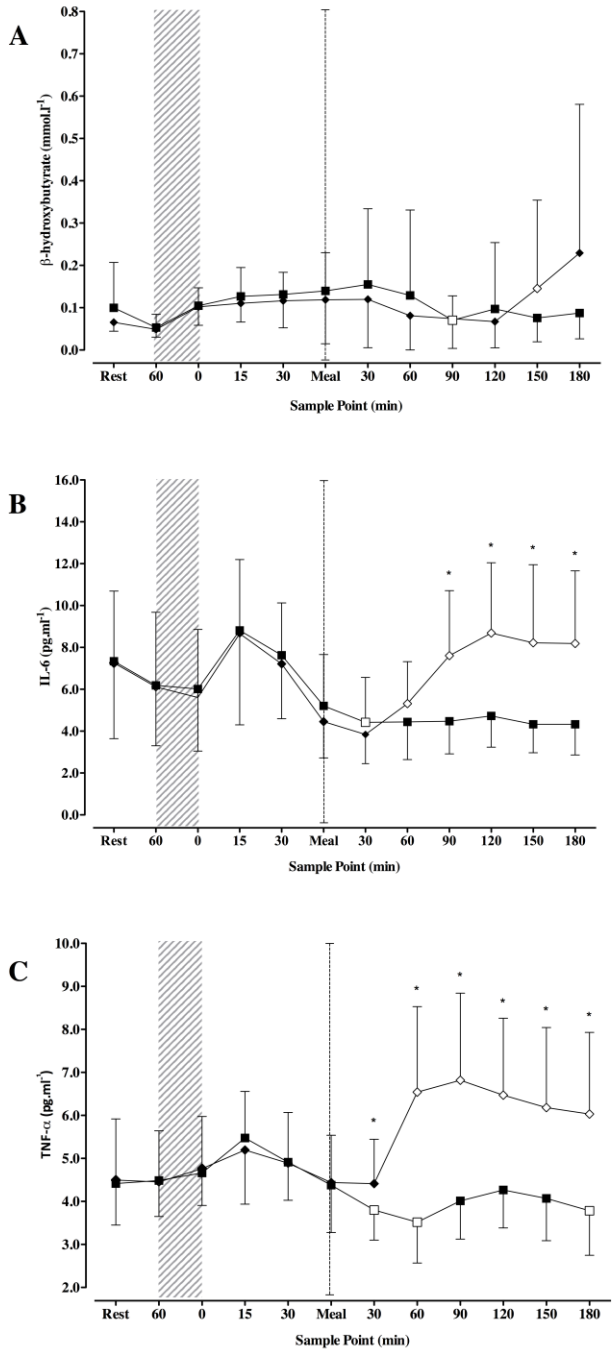

Figure 2. (**A**) Time-course changes in serum β-hydroxybutyrate, (**B**) plasma IL-6 and (**C**) plasma TNF-α. Data are presented as mean ± SEM error bars. Squares = **LGI**, diamonds = **HGI**. Transparent markers indicate significant difference from pre-meal concentrations ($p \leq 0.05$). * indicates significant difference between conditions ($p \leq 0.05$). Thatched area indicates exercise; vertical dashed line indicates post-exercise meal intervention. NOTE: Test meal and insulin were administered immediately following rest and 60 minutes post-exercise sample points.

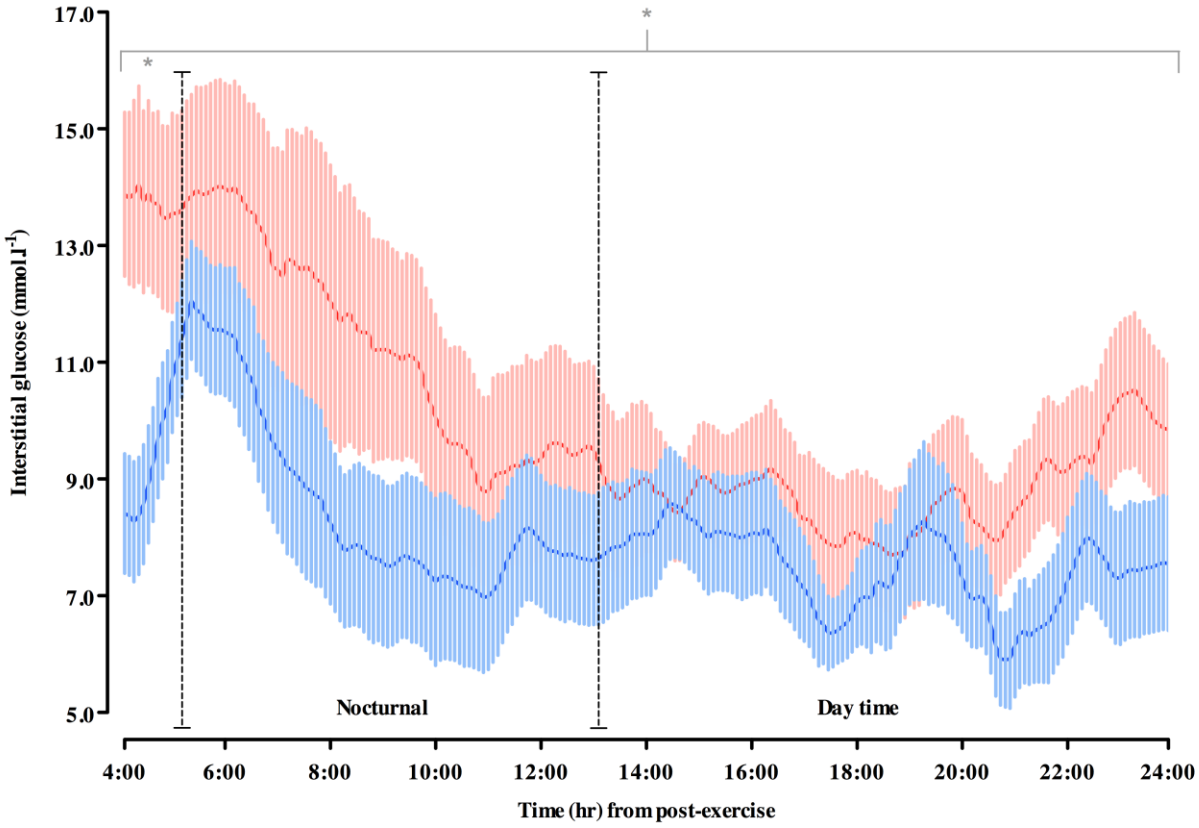

Figure 3. Time-course changes in interstitial glucose throughout the post-laboratory period. Data are presented as mean ± SEM. Red trace = **HGI**, blue trace = **LGI**.* indicates interstitial glucose area under the curve is significantly different between conditions ($p \leq 0.05$). Vertical dashed lines indicates nocturnal or day-time periods. End of nocturnal period indicates when patients awoke.